

Clinical and magnetic resonance imaging findings of a cerebellar medulloblastoma in a heifer

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Key Clinical Message

Reports of medulloblastoma in cattle are scarce; however, this neoplasm should be included as a differential diagnosis in cases of cerebellar or central vestibular signs in young cattle. The MRI appearance of the medulloblastoma reported here, previously unreported in cattle, consisted of a T1-weighted hypointense and T2-weighted heterogeneously hyperintense intra-axial mass.

KEY WORDS

advanced imaging, cattle, cerebellum, embryonal neoplasia

1 | CASE HISTORY

A 9-month-old, Shorthorn cross heifer was presented with a four-month static history of incoordination and head tilt. The animal was reported to be normal at birth. Neurological signs were first observed following an episode of pneumonia when the heifer was five months old. Following treatment and resolution of pneumonia, lack of resolution of the neurological signs prompted referral.

On physical examination, the heifer was in good body condition. Neurological examination demonstrated normal mental status, broad-based stance, right head tilt and

pleurothotonus, tendency to circle to the right, generalized ataxia with slight hypermetria in the right thoracic and pelvic limbs, and normal hoof replacement responses. Segmental spinal reflexes could not be assessed due to severe balance loss. On cranial nerve evaluation, a decreased menace response in the right eye and positional rotatory nystagmus with the fast phase to the right were found.

Neuroanatomic localization of clinical signs was consistent with a lesion to the central vestibular system, primarily right cerebellum. The primary differential diagnoses included malformation (eg, hamartoma, dermoid cyst in the caudal fossa), neoplasia (eg, medulloblastoma, ependymoblastoma,

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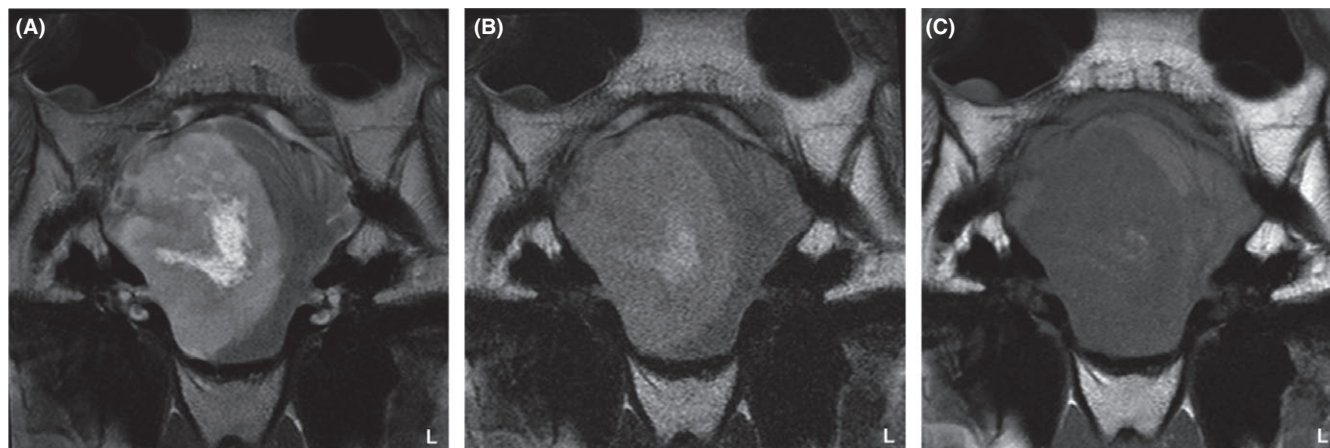


FIGURE 1 Immediate postmortem transverse T2-weighted (A), FLAIR (B), and T1-weighted (C) MR images of the cerebellum of a 9-month-old Shorthorn cross heifer showing a large right-sided well-defined smoothly margined intra-axial mass replacing more than two thirds of the normal cerebellar parenchyma

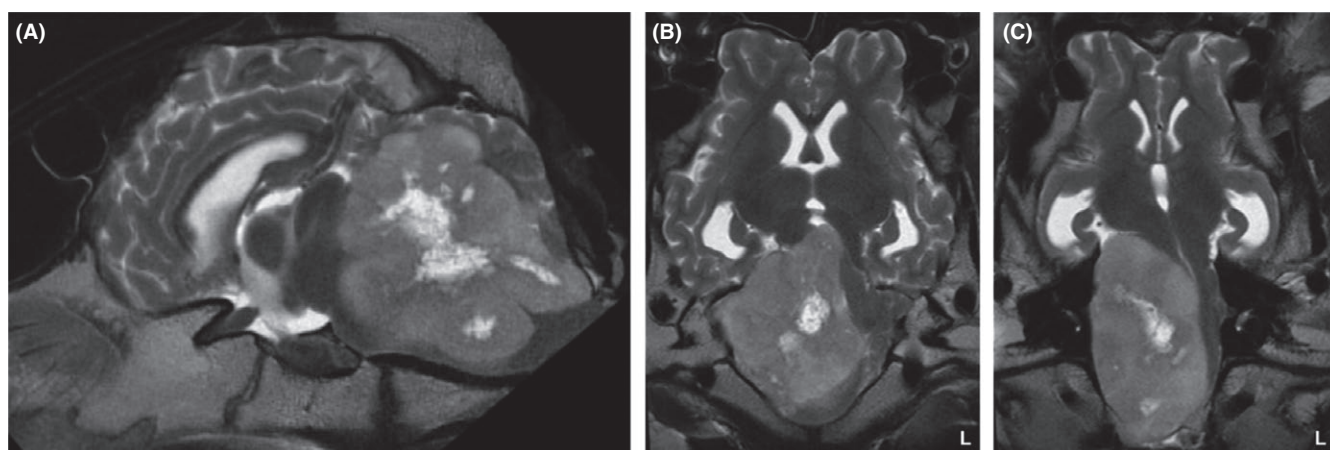


FIGURE 2 Immediate postmortem midsagittal (A) and dorsal (B-level of the dorsal third ventricle; C-level of the mesencephalic aqueduct) T2-weighted MR images of the brain of a 9-month-old Shorthorn cross heifer showing severe mass effect on the thalamus and brainstem associated with the cerebellar mass

malignant ependymoma, glioma), and less likely, infectious (eg, intracranial abscess, listeriosis).

Neurological signs remained static two months following admission at which stage the heifer was humanely euthanized because of the poor prognosis.

Immediate postmortem magnetic resonance imaging (MRI) was performed using a 1.5 Tesla magnet (Siemens Magnetom Essenza, Siemens, Camberley, UK). The head was placed in a head and neck coil in prone position immediately after decapitation following euthanasia. T2-weighted turbo spin echo sequences were obtained in the sagittal, dorsal, and transverse planes. Transverse T1-weighted spin echo, fluid attenuation inversion recovery (FLAIR), T2*-weighted, 3D-volumetric interpolated breath-hold examination, and dorsal 3D-constructive interference steady-state sequences were also acquired. It was not possible to obtain contrast-enhanced T1-weighted images due to MRI study acquired postmortem.

A very large, smoothly margined and lobulated intra-axial mass was present within the right side of the cerebellum, replacing more than two thirds of the normal cerebellar parenchyma. On T2-weighted, FLAIR, and 3D-constructive interference steady-state sequences, the mass was heterogeneously hyperintense to normal gray matter in the periphery, with an irregular ill-defined markedly hyperintense core (Figure 1A,B). The mass was heterogeneously hypointense to normal gray matter on T1-weighted and 3D-volumetric interpolated breath-hold examination images, with small irregular hyperintense foci in the center (Figure 1C). No signal void was present within the mass on T2*-weighted images. A severe mass effect was present causing obstructive hydrocephalus, and the lateral and third ventricles displayed moderate enlargement (Figure 2) and mild periventricular edema on FLAIR images. Severe dorsoventral compression and left-sided displacement of the brainstem (Figure 2C) and

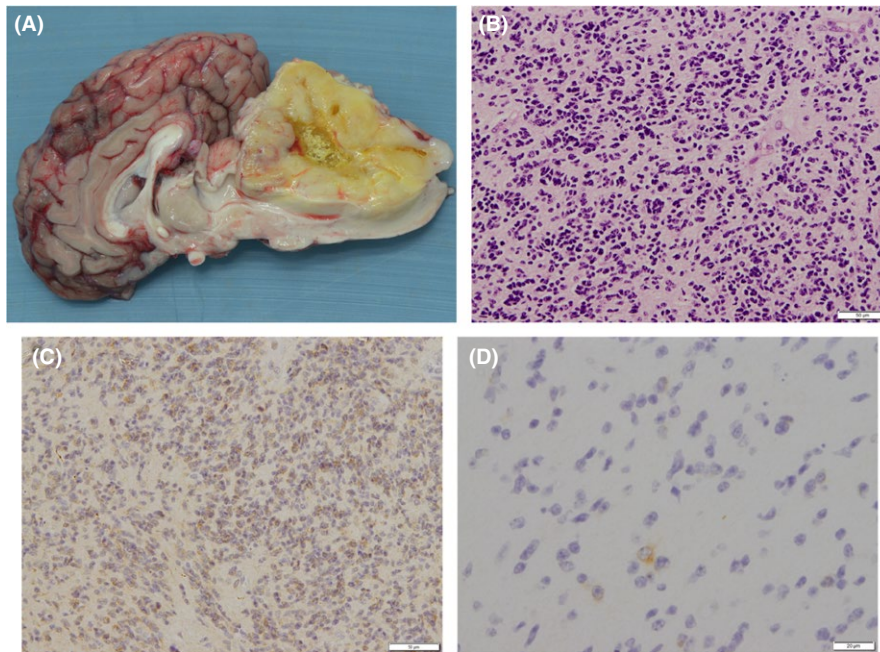


FIGURE 3 A, Unfixed median section of the brain of a 9-month-old heifer revealing a firm, pale cream to yellow, homogeneous and lobulated intra-axial mass in the cerebellum with a central, focal, 1.5 cm ovoid necrotic cavity containing pale to straw yellow colored transparent fluid. B, Photomicrograph demonstrating sheets of moderately densely packed small neoplastic cells. H&E stain; scale bar: 50 μ m. C, Immunohistochemically, the majority of neoplastic cells within densely cellular nodular areas of the neoplasm show moderate cytoplasmic staining with NSE. Scale bar: 50 μ m. D, Approximately 10% of neoplastic cells showed weak to moderate staining with synaptophysin. Scale bar: 20 μ m. H&E, hematoxylin-eosin; NSE, neuron-specific enolase

caudo-rostral brain shift with associated rostral transtentorial herniation of the cerebellum were present. One of the mass lobules was also herniating through the foramen magnum (Figure 2A). The MRI findings were most likely consistent with a neoplastic process (eg, medulloblastoma, glioma, ependymoma, ependymoblastoma).

Gross pathological examination of the brain identified extensive effacement of the cerebellum surface by a firm, pale cream to yellow, homogeneous and lobulated intra-axial mass which replaced up to 50% of the right side of the cerebellum. On longitudinal sectioning, the normal distinction between gray and white matter at the arborvitae was replaced by a central, focal, 1.5 cm diameter, ovoid defect containing pale to straw yellow transparent fluid, with a small hemorrhagic area in its rostral margin (Figure 3A). There were multiple extensions to the leptomeninges and the rostral medullary vellum. Marked compression of the underlying pons and medulla oblongata was also noted; however, no signs of infiltration of the ventricular system were seen. Tissue was collected and fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4 μ m, and stained with hematoxylin and eosin for histopathological analysis. Multiple immunohistochemical stains were performed. For this, sections of formalin fixed, paraffin-embedded tissues, and 4 μ m in thickness were deparaffinized and rehydrated, and heat-induced epitope retrieval (Access Retrieval Unit, Menarini Diagnostics Ltd, Winnersh, UK) was performed or enzymatic antigen

retrieval with proteinase K (Proteinase K Ready-to-use, Dako, Glostrup, Denmark) and stained using an autostainer (Dako Autostainer Plus Staining System, Dako, Glostrup, Denmark). Visualization of staining with the primary antibody was by using a horseradish peroxidase-conjugated secondary antibody (EnVision+System-HRP Labelled Polymer Anti-Rabbit, Dako, Glostrup, Denmark). The primary antibodies used, together with the supplier and dilution, are listed in Table 1.

Histological examination revealed extensive effacement of normal tissues by an unencapsulated, variably well-demarcated, infiltrative neoplasm. Focally, the mass appeared to arise from within or adjacent to the external granular layer of the cerebellum. Within the mass, there were variably sized poorly demarcated nodules of moderately densely packed small, neoplastic cells arranged in sheets separated by less densely cellular areas supported by neurofibrillary stroma (Figure 3B). Within nodular areas, neoplastic cells had oval to round nuclei with densely basophilic chromatin, often with a prominent nucleolus and scant pale eosinophilic cytoplasm. There was mild to moderate anisokaryosis, and a mitotic rate of two mitoses in 10 high power fields (400x) was counted. Multifocally, blood vessels were hyperplastic throughout the mass and were lined by several layers of proliferative plump endothelial cells. There were multifocal cavitated, variably sized areas of necrosis within the mass that were filled with eosinophilic or partially mineralized debris. Overall, between

TABLE 1 Details of immunohistochemical reagents used to evaluate the cerebellar neoplasia

Target antigen	Type of antibody (clone if mAb)	Pretreatment	Secondary antibody	Dilution (1in)	Supplier
NSE	mAb BBS/NCX/VI-H14	HIER	Mouse	1000	Dako
Synaptophysin	pAb	HIER	Rabbit	150	Dako
Chromogranin A	pAb	HIER	Rabbit	1500	Dako
GFAP	pAb	HIER	Rabbit	16 000	Dako

NSE, neuron-specific enolase; GFAP, glial fibrillary acidic protein; HIER, heat-induced epitope retrieval; mAb, monoclonal antibody; pAb, polyclonal antibody.

30% and 50% of neoplastic cells showed some cytoplasmic staining with neuron-specific enolase (NSE) (Figure 3C). Staining was quite variable, with almost complete staining in nodular areas of the neoplasm, and weak to no staining was seen in more sparsely cellular areas. Neoplastic cells did not stain with glial fibrillary acidic protein (GFAP) or chromogranin A, and weak cytoplasmic staining was seen in up to 10% of neoplastic cells with synaptophysin (Figure 3D). Immunohistochemical staining was supportive of neuronal differentiation, making glioma, ependymoma, and ependymoblastoma unlikely. Based on the gross appearance of this tumor as a well-defined mass within the cerebellum in a young bovine, together with the histopathological appearance, immunohistochemical staining with markers for neuronal differentiation characterized the tumor as a medulloblastoma.

2 | DISCUSSION

Medulloblastoma has been reported in dogs, cats, ruminants, and pigs with a consistent higher prevalence in young animals in all species.¹ Arising in the cerebellum, medulloblastomas are an invasive malignant embryonal neuroepithelial neoplasia (also known as cerebellar primitive neuroectodermal tumor) that commonly metastasize via the cerebrospinal fluid system in humans.²

Reports of medulloblastoma in cattle are scarce; it has been described in two Aberdeen Angus, one Hereford, one Australian Shorthorn, one Aberdeen Angus crossbreed, one Holstein, one Piedmontese, and two crossbreed calves.³⁻⁸ Commonly, animals display an ataxic gait. Opisthotonus and inability to stand have also been reported, and usually animals show lateralized neurological signs to different degrees. In this case, the heifer showed clinical signs mainly compatible with a lesion in the right cerebellum. With unilateral lesions, the clinical signs of cerebellar ataxia are ipsilateral with spasticity, hypermetria, and variable postural reaction deficits.⁹ Disturbance of the vestibular system components of the cerebellum may cause balance loss and head tilt toward or away from the site of the lesion. Further to that, involvement of the flocculonodular lobe or fastigial nucleus of the cerebellum can cause signs of abnormal nystagmus, broad-based stance, and staggering

gait. However, with flocculonodular lobe involvement, the head tilt is contralateral to the lesion (paradoxical central vestibular syndrome), differently from the present case. Animals with significant cerebellar disease often fail to respond to the menace test in the presence of normal vision and facial muscle function, especially when the interpositional and lateral cerebellar nuclei are involved. Menace response has only been evaluated in a previously reported case of bovine cerebellar medulloblastoma revealing ipsilateral deficits as in the case reported herein. Potential thalamic involvement was discussed in this case due to the presence of pleurothotonus, which consists of head and neck turning to one side (usually toward the side on which the lesion exists). This is commonly associated with rostral thalamic lesions.^{9,10} Although there was no direct involvement of the thalamus in the case reported here, pleurothotonus might have been secondary to thalamic distortion/compression due to mass effect and caudo-rostral brain shift and/or related to compression of the ipsilateral medial longitudinal fasciculus within the brainstem.¹⁰ Interestingly, pleurothotonus has also been described in a report from 1940 of seventeen rabbits following a lesion in the cerebellar medial zone and consequent destruction of the fastigial nucleus.¹¹

Due to the increased availability of MRI in veterinary medicine, MRI findings of medulloblastoma have been reported in some species; however, this is the first description of the MRI characteristics of cerebellar medulloblastoma in the bovine species to the authors' knowledge. Two cases of feline cerebellar medulloblastoma have been reported, including MRI evaluation.^{12,13} In both cases, the tumor was described as a hypointense mass relative to normal gray matter on T1-weighted sequences, with or without hyperintense foci. MRI evaluation of canine cerebellar medulloblastomas led to slightly different results. In an Airedale terrier, the mass was generally T1-weighted hypointense to normal gray matter while in a Polish Lowland Sheepdog, the cerebellar medulloblastoma was mainly isointense on T1-weighted images with multiple focal areas of low signal and some hyperintense foci in the caudal part of the mass, likely corresponding to hemorrhagic areas seen on postmortem examination.^{14,15} In our case, the lesion was mainly hypointense on T1-weighted images with few hyperintense foci in its core, coinciding with the region of hemorrhage observed on gross examination. In a

case series of human medulloblastoma, results of T1-weighted sequences were as varied as above; when the intensity of the neoplastic mass was compared to normal gray matter, 48% of tumors were hypointense, 32% were isointense, and 20% had a mixed signal intensity, whereas 96% of the tumors were hypointense when compared to white matter.¹⁶

A certain degree of variability is also reported on T2-weighted images. The tumor appeared poorly defined and mildly hyperintense in a Bassett Hound while of mixed intensities with hypointense and hyperintense areas in a cat.^{12,17} However, it was predominantly hyperintense to normal gray matter with multiple focal areas of high signal on another feline and two canine patients. These areas were correlated with intratumoral necrotic foci on histopathological examination.¹³⁻¹⁵ In this heifer, MRI characteristics were similar as the mass was heterogeneously T2-weighted hyperintense with a markedly hyperintense core, which was described on postmortem examination as a central, focal, cavitated area of necrosis.

Postcontrast images were not obtained in this case as a consequence of MRI sequences being obtained postmortem. Postcontrast T1-weighted images have been already described in different species such as human, dogs, and cats.^{12,14-17} In the human literature, various types of enhancement are encountered in medulloblastoma cases, from diffuse homogenous enhancement to minimal heterogeneous or no enhancement.¹⁸ In one human report, medulloblastoma tumoral masses showed heterogeneous contrast enhancement in all patients, after administration of contrast medium.¹⁶ Similar findings have been described in dogs and in a cat with medulloblastomas showing different types of enhancement.^{12,14,15}

In humans, the most common intra-axial pediatric posterior fossa neoplasms, along with medulloblastomas, include juvenile pilocytic astrocytoma and ependymomas.¹⁹ Glial tumors have been sparsely reported in young animals in the veterinary literature.²⁰ These tumors have been more frequently reported in adult animals in which they usually affect the forebrain.²¹⁻²³ Equally ependymoma was considered a possible differential diagnosis given the MRI characteristics; however, this type of tumor has been more commonly reported in adult patients in the veterinary literature.^{24,25} Ependymoblastoma has only been reported once in cattle, and its MRI features have been recently described in humans consisting of well-defined tumor margins, iso- to hyperintense tumor signal relative to gray matter on T2-weighted images, mainly hypo- to isointense signal on T1-weighted images although different signal intensities (hypo-/iso-/hyperintense) can be found due to partial hemorrhage and calcifications, and mild to moderate contrast enhancement.^{26,27} Although ependymoblastoma was considered compatible with our findings, it was deemed less likely in view of its rarity.

The gross postmortem appearance of medulloblastoma is usually described as a soft, well-defined mass,

grayish to reddish in color, and widely variable in size.^{1,3,5,6} Medulloblastoma in cattle, with the sole exception of one report, has been reported to develop unilaterally in the dorso-lateral aspect of the cerebellum, involving one hemisphere and the cerebellar vermis.³ In most of the bovine cases reported the tumor infiltrated the surrounding structures and occasionally occluded the fourth ventricle.^{3,4,7} In the present report, the pathological findings are consistent with those reported in the literature. The tumor replaced about 50% of the right side of the cerebellum involving the whole right hemisphere and vermis. Grossly, the mass appeared relatively well demarcated, compressing surrounding structures.

Histopathology results characterized the tumor as a medulloblastoma, an embryonal tumor of neuroepithelium. The microscopic appearance of medulloblastoma is reported as densely cellular masses arranged in sheets or nodules with oval to carrot-shaped nuclei and minimal cytoplasm. The mitotic rate is often quite high, and neuroblastic Homer-Wright rosettes are sometimes formed but are considered an uncommon feature.^{2,28} In this case, the classic Homer-Wright rosettes were not seen, and the location in the cerebellum and focal staining with neuronal markers were used to identify the tumor.²⁹ Reactivity of medulloblastomas for neuronal markers depends on the degree of tumor differentiation, and staining with these markers is not a consistent finding in all cases.²⁸ As NSE staining has been reported to be a less reliable marker, synaptophysin and other markers which were not available in this case (neuron-specific nuclear protein and microtubule-associated protein 2) have been recommended to further assist the diagnosis of this tumor.²⁸

3 | CONCLUSION

Cerebellar medulloblastoma should be considered as a differential diagnosis in young cattle with cerebellar or central vestibular disease. The MRI appearance of the medulloblastoma reported here was consistent with previously reported MRI features in the human and veterinary literatures, being T1-weighted hypointense with few hyperintense foci, and heterogeneously T2-weighted and FLAIR hyperintense to normal gray matter with a markedly hyperintense center.^{12,13,16,17} To the authors' knowledge, this is the first description of the MRI features of medulloblastoma in cattle.

CONFLICT OF INTEREST

This work was not supported by any grant, and none of the authors of this paper have conflict of interests that could influence the content of the paper.

AUTHOR CONTRIBUTION

AF: collected the information and was the writer of the manuscript. AD: produced the magnetic resonance imaging figures and their descriptions and contributed to the writing of the manuscript. LV: contributed to the evaluation and management of the patient and reviewed the manuscript. JO: contributed to the evaluation and management of the patient and reviewed the manuscript. CM: assessed the histopathology, provided the neuropathology images and their descriptions, and contributed to the writing of the manuscript. RJL: contributed to the evaluation of the patient, produced the neuropathology figure, and contributed to the writing of the manuscript.

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